

PATENT COOPERATION TREATY

RECEIVED

OCT 17 2005

From the INTERNATIONAL SEARCHING AUTHORITY

To:
JANE MASSEY LICATA
LICATA & TYRRELL PC
66 E. MAIN STREET
MARLTON, NJ 08053

Docket System
Status Report
Docket Book

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

<p>Applicant's or agent's file reference WSTR-0020B</p> <p>International application No. PCT/US04/19603</p> <p>Applicant THE WISTAR INSTITUTE</p>	<p>Date of mailing (day/month/year) 13 OCT 2005</p> <p>FOR FURTHER ACTION See paragraphs 1 and 4 below</p> <p>International filing date (day/month/year) 18 June 2004 (18.06.2004)</p>
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1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ **With regard to the protest against payment of (an) additional fee(s) under Rule 40.2,** the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

<p>Name and mailing address of the ISA/ US</p> <p>Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450</p> <p>Facsimile No. (703) 305-3230</p>	<p>Authorized officer</p> <p>Ram Shukla </p> <p>Telephone No. (571) 272-0735</p>
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Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference WSTR-0020B	FOR FURTHER ACTION <small>see Form PCT/ISA/220 as well as, where applicable, item 5 below.</small>	
International application No. PCT/US04/19603	International filing date (<i>day/month/year</i>) 18 June 2004 (18.06.2004)	(Earliest) Priority Date (<i>day/month/year</i>) 18 June 2003 (18.06.2003)
Applicant THE WISTAR INSTITUTE		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (See Box No. III)

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____



as suggested by the applicant.



as selected by this Authority, because the applicant failed to suggest a figure.



as selected by this Authority, because this figure better characterizes the invention.

- b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/19603

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : C12N 15/00, 15/11, 15/09; A61K 48/100 US CL : 536/23.1; 435/320.1; 514/44 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 536/23.1; 435/320.1; 514/44 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	YAROSH et al. Human adenovirus type 5 vectors expressing rabies glycoprotein. Vaccine. 1996. vol. 14, no. 13, pages 1257-1264, see entire document	1-22
Y	KANELLOS et al. Naked DNA when co-administered intranasally with heat-labile enterotoxin of Escherichia coli primes effectively for systemic B-an T-cell responses to the encoded antigen. Immunology Letters. 2000. Vol. 74, pages 215-220, see entire document	1-22
Y	LEITNER et al. Nucleic Acid for the treatment of cancer:Genetic Vaccines and DNA Adjuvants. Current Pharmaceutical Design. 2001, vol. 7 pages 1641-1667, see entire document	1-22
Y	VELIN et al. Delivery Systems and Adjuvants for Vaccination against HIV. Pathobiology. 1998. Vol. 66, no. 3/4, pages 170-175, see entire document	1-22
A	GILBERT et al. Enhanced CD8 T cell immunogenicity and protective efficacy in a mouse malaria model using a recombinant adenoviral vaccine in heterologous prime-boost immunisation regimes. Vaccine 2002. vol. 20, pages 1039-1045,see entire document	1-22
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search 25 July 2005 (25.07.2005)		Date of mailing of the international search report 13 OCT 2005
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230		Authorized officer Ram Shukla Telephone No. (571) 272-0735

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/19603

Continuation of B. FIELDS SEARCHED Item 3:

EAST: USPAT, USPGPUB, DERWENT, EPO

STN:FILE Medline

Search terms:adenovirus, vaccine, nucleic acid encoded adjuvant, CpG, oral, prime boost

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
JANE MASSEY LICATA
LICATA & TYRRELL PC
66 E. MAIN STREET
MARLTON, NJ 08053

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference WSTR-0020B		Date of mailing (day/month/year) 13 OCT 2003
FOR FURTHER ACTION See paragraph 2 below		
International application No. PCT/US04/19603	International filing date (day/month/year) 18 June 2004 (18.06.2004)	Priority date (day/month/year) 18 June 2003 (18.06.2003)
International Patent Classification (IPC) or both national classification and IPC IPC(7): C12N 15/00, 15/11, 15/09; A61K 48/100 and US Cl.: 536/23.1; 435/320.1; 514/44		
Applicant THE WISTAR INSTITUTE		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

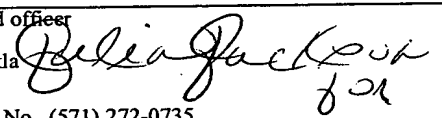
2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Ram Shukla  Telephone No. (571) 272-0735
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US04/19603

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

- ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

- ☐ a sequence listing
☐ table(s) related to the sequence listing

b. format of material

- ☐ in written format
☐ in computer readable form

c. time of filing/furnishing

- ☐ contained in international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US04/19603

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-22	YES
	Claims <u>NONE</u>	NO
Inventive step (IS)	Claims <u>NONE</u>	YES
	Claims 1-22	NO
Industrial applicability (IA)	Claims 1-22	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Claims 1-22 lack an inventive step under PCT Article 33(3) as being obvious over YAROSH et al. Human adenovirus type 5 vectors expressing rabies glycoprotein. Vaccine. 1996. vol. 14, no. 13, pages 1257-1264, in view of KANELLOS et al. Naked DNA when co-administered intranasally with heat-labile enterotoxin of *Escherichia coli* primes effectively for systemic B-an T-cell responses to the encoded antigen. Immunology Letters. 2000. Vol. 74, pages 215-220, and LEITNER et al. Nucleic Acid for the treatment of cancer: Genetic Vaccines and DNA Adjuvants. Current Pharmaceutical Design. 2001, vol. 7 pages 1641-1667.

YAROSH et al. provides guidance on the administration of human adenovirus vectors expressing rabies glycoprotein to mice and skunks (Abstract; pg. 1259, col. 1, materials and methods). Wherein the adenovirus was administered to the mice by i.p. injection and to the skunks by oral vaccination (pg. 1259, col. 1, materials and methods). Further, YAROSH et al. teaches that both routes of administration were able to induce immunization in the host animals (pg. 1261, Table 1; pg. 1262, Table 2).

KANELLOS et al. supplements the guidance provided by YAROSH et al., by teaching a prime-boost strategy of inducing mucosal immunization with plasmid DNA's encoding LacZ and heat labile enterotoxin as an adjuvant (Abstract). Wherein the first dose is administered intranasally, followed at a later date by i.p. administration of the same plasmid DNA (Abstract, pg. 215, Materials and Methods).

LEITNER et al. supplements the guidance provided by YAROSH et al., by teaching that the removal of neutralizing CpG motifs and the addition of immunostimulatory CpG motifs found on a bacterial backbone enhances the immunogenicity of adenoviral vectors (pg. 1660, col.2, pgph 1).

Based on the guidance provided by YAROSH et al. supplemented with the teachings of KANELLOS et al. and LEITNER et al. it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the adenoviral vector by adding CpG motifs so that the vector encoded an adjuvant. Further it would have been obvious to administer the adenovirus vaccine of YAROSH et al. more than once, either orally first then via i.p. administration, or vice versa. Such changes in administration would have been routine in the art at the time of filing.

The practitioner would be motivated to adjust the CpG motifs of the adenoviral vector in order to increase its immunogenicity. Further the practitioner would have been motivated to use a prime boost method of administering the vaccine via both orally and i.p. routes of administration in order to maximize the immune response.

The person of ordinary skill in the art would have a reasonable expectation of success because modifying the adenoviral vector and increasing the number of times it was to be administered would have been routine and minor modifications in the art at the time of filing.

Claims 1-22 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.